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ORIGINAL ARTICLES.

THE THERAPEUTICS OF DIGITALIS AND ITS ALLIES.[1]

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In 1775, William Withering, a Birmingham physician, had his attention drawn to a family receipt for the cure of dropsy long kept secret by an old woman in Shropshire; he found it composed of some twenty herbs, of which he concluded that foxglove was the essential one. After trying it in his practice for some months he "ventured to assert" that this herb "merited more attention than modern practice bestowed on it." These were the days of deliberate observation in medicine however, and it was not until after ten years careful use of it in his practice that he gave his results to the world,[2] although he had induced many of his friends to use it in the meantime. In his "account of the foxglove," he recognizes its action on the heart,[3] but is chiefly interested in its diuretic effects, and does not associate the latter with the cardiac changes. Withering's work directed immediate attention to the new remedy; I find it given an assured place by Barton, of Philadelphia, in 1798. But its true sphere of action was obscured by its being recommended as a cure for phthisis, although its dis-

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[1] An address delivered before the Harvey Society of New York, January 14, 1911.

[2] An account of the foxglove, and some of its medical uses with practical remarks on dropsy and other diseases. By William Withering, M.D., Birmingham, 1785. This work bears the appropriate motto *nonumque prematur in annum*, and ought to receive attention as an example of the careful observation of the time; it may be added that it may help to dispel some of the apprehensions of the "cumulative" and other dangerous effects of digitalis which are too prevalent.

[3] "It has a power over the motion of the heart to a degree yet unobserved in any other medicine and this power may be converted to salutary ends," p. 192.

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coverer denied it any usefulness in this disease from the beginning. Later it slowly resumed its position as the cardiac remedy par excellence, but curiously enough not as a cardiac tonic, but as a depressant. Sixty years after its introduction into regular medicine Pereira, the great authority of his day, recommended it chiefly "to reduce the force and velocity of the circulation" as in aneurysm and hemorrhage of internal organs. In his time the new method of experimental investigation of the effects of drugs on animals was in its infancy, but it was soon afterward applied to digitalis by Traube, Schmiedeberg, and others, and the action of digitalis and its allies on the organism was ascertained with certainty in many respects, although it still requires further elucidation. The knowledge of its therapeutic use has also advanced since Pereira's time, and few would venture to recommend digitalis in hemorrhage and still fewer in aneurysm at the present time. But this advance in the therapeutic applications has scarcely kept pace with that of the experimental investigation. Too often the diagnosis of cardiac abnormality, the discovery of a murmur, is regarded as an immediate indication for digitalis, so that in the narrower sphere of the circulatory diseases, digitalis suffers today from the same over-appreciation as was its fate a hundred years ago, when to some minds it appeared to be a panacea for all internal disorders. The advance in the diagnosis of heart disease in recent years, however, gives hope that the sphere of action of digitalis may be more circumscribed, and that we may soon reach a point where instead of "trying digitalis" in every case of heart disease we may be able to define the symptom complex which indicates its exhibition as accurately as that for quinine.

It has long been my feeling that the study of experimental pharmacology should be merely the preliminary to investigation in therapeutics, and I very gladly accepted the invitation of my friend Dr. James Mackenzie to associate myself with him in his clinical researches on the effects of drugs on the circulation. Our final object is to differentiate the types of heart disease in which digitalis is useful, and I may say at once that some progress has been made in this direction. Incidentally we have carefully noted the effect of digitalis and its allies on the human heart and circulation with the view that one or the other might be preferable in certain conditions. We are still far from achieving our goal, but a certain amount of information has been acquired, and when your president did me the honor of asking me to address you, I thought that nothing I could offer would be more appropriate to a society that honors the great name of Harvey than a contribution to the therapeutics of the great remedy in diseases of the circulation.

In the experimental laboratory it is found that digitalis affects the heart in several different directions. In the first place, it was recognized early by Traube that the heart is slowed by stimulation of the inhibitory centre in the medulla. Since his time inhibition of the heart has been shown to depress not only the rate, but also the strength of contraction, the conductivity and the tone of the muscle, so that these must be taken into consideration in any account of the changes induced by the drug. On the other hand, digitalis acting directly on the heart muscle increases the strength of contraction, the tone and the excitability. Its direct effects on conductivity have not been accurately determined. The effects of digitalis on the mammalian heart are, therefore, compounded of two influences which in most instances oppose each other. The rhythm is slowed by the inhibition and accelerated by the muscular action, but in moderate quantities in animals the former prevails and the rhythm is slower. The strength of contraction and the tone are reduced by the inhibitory stimulation and increased by the direct action on the heart, and the changes observed are the resultant of these two; in the ventricle the muscular effect prevails and the chamber beats more strongly, and at any rate, in the dilated heart, relaxes less than before the administration. In the auricle, the inhibitory prevails over the muscular factor, and the result is a decrease in the strength of contraction very often, or it may be there is little change to be noted in this chamber from digitalis. In animals the blood pressure rises from contraction of the arterioles which are acted on direcctly by the glucosides.

In these experiments in animals, the drugs are injected intravenously in order to elicit the effects quickly enough to permit of their being observed within the limits of an experiment of at most three to four hours' duration. In the therapeutic use of digitalis, however, one seldom sees much change from the drug under thirty-six to forty-eight hours. In addition, the dose given experimentally is often very much larger in proportion than that in therapeutic use, and this, together with the rapidity with which it is thrown into the circulation, must cause a much greater concentration in the blood than is induced in therapeutics. Great caution must, therefore, be used in applying the results obtained experimentally in therapeutics, and perhaps this has not been sufficiently appreciated; I cannot cast a stone at any one. But these experimental investigations, at any rate, show that inhibition and muscular action may be elicited in animals by this series, and encourage us to look for these effects in man.

In Dr. Mackenzie's clinic the patients are, of course, examined by his well-known methods, and the course of the disease and the effects of treatment are constantly controlled by graphic tracings in addition to the ordinary clinical notes. Conclusions may, therefore, be drawn with some confidence from a small number of cases. The disorders of the heart were all of such seriousness as to necessitate admission to hospital and detention there, often for months at a time. The treatment with digitalis was almost always preceded by rest in bed for a week or more in order to eliminate as far as possible the error of attributing to the drug changes really due to the general conditions. The disorders of the heart on which we have made our observations, may be conveniently thrown into two great groups: (1) Those in which the dominant rhythm of the heart continued to originate in the normal point (Keith-Flack node), and (2) those in which the rhythmogenic function was usurped by some other part of the heart, in our cases by the auricle. The effects of digitalis are so different in these two groups that I shall describe them separately.

In the first group digitalis often caused considerable improvement in the general condition, manifested in relief of the dyspnœa or dropsy, or lessened cyanosis, though the benefit was much less obvious than in the second group of cases. This improvement in the general condition was sometimes accompanied by moderate slowing of the pulse which fell from 90 to 110, to 70 to 80 per minute. But this is by no means elicited in every case even when the other symptoms are relieved. Thus, of 18 patients of the first group, only 6 showed any slowing under digitalis, and in one of these it may be questioned whether this was due to the drug. We can safely say that the pulse was slowed by digitalis in only about 30 per cent. of the cases in which the dominant rhythm was of normal origin. In 2 of our 6 cases, the pulse was previously very rapid and it is possible that excessive activity of the rhythmogenic node may favor this effect of digitalis; on the other hand, if this excessive activity arises from fever digitalis often fails to induce slowing. In the other cases in which slowing followed the use of digitalis no feature was observable which distinguished them from those in which no such effect occurred. During the slowing the heart beat continued to bear its ordinary character; in other words, the slowing is due to fewer impulses being emitted by the rhythmogenic area.

The slowing of the heart under digitalis is universally attributed to stimulation of the inhibitory centre in the medulla oblongata, and in fact it bears every resemblance to the effects of such stimulation. Thus the slowing is not uniform, the rhythm varying with the phases of respiration, as it does in normal individuals with marked inhibition. And this respiratory variation may be developed under digitalis in persons in whom it is previously absent or hardly perceptible. Owing to the development of this feature, the intervals between successive pulse beats may show larger variations after digitalis than before, as Wenckebach has recently pointed out, although perhaps his description tends to exaggerate the significance of this feature.

Further evidence that the slowing is inhibitory in origin is offered by the observation that it disappears under doses of atropine which have no further effect than to prevent the inhibitory impulses reaching the heart. And finally it has been noted that in complete block, digitalis does not slow the ventricle as might be expected if it retarded the heart by direct action on the ventricular muscle, while the auricle continues to be slowed as in the normal heart.

The question arises why digitalis fails in so many instances to slow the heart. We may exclude at once inactivity of the drug because our preparations were assayed pharmacologically and on treating two patients with the same tincture in the same doses, the one may respond by marked slowing, while the other shows no such effect even when the drug is pushed until nausea and vomiting are produced. Either the centre in the medulla is incapable of stimulation in these recalcitrant cases, or it is incapable of holding the heart in check. It is known that the control ordinarily exercised by the inhibitory centre over the heart varies in different individuals and at different ages in the same individual, and evidence is not wanting that the resistance of the heart to the maximal activity of the centre also varies in the same way. In many instances this resistance is great enough to render nugatory the increased activity of the inhibition induced by digitalis; this resistance to inhibition is especially marked in cases of fever, more particularly when the infection is located in the heart muscle itself as in active myocarditis, in which the irritability of the heart must be considered abnormally augumented.

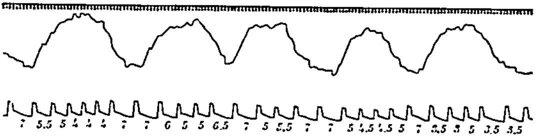

FIG. 1.—Tracing of the respiration (upper) and radial pulse (lower) in patient under digitalis, showing sinus arrythmia.

When digitalis is pushed further in susceptible cases, the inhibition becomes more marked, and obvious irregularities may appear. One of these, like the general slowing, arises from inhibition of the rhythmogenic area—the sinus irregularity, as it has been called. It often occurs without drugs, and consists in alternate phases of slowing and quickening of the heart corresponding to the inspiration and expiration, and is generally attributed to the inhibitory cardiac centre being involved in the stimulation of the respiratory centre; the stimulus is said to spread to the inhibitory centre. The sinus irregularity of digitalis is sometimes of the same kind, the slowing and quickening corresponding to the movements of respiration fairly closely (Fig. 1). In most cases however, this does not hold, the phase of slowing recurring at intervals which are much longer than those of respiration. Here one may suppose that the excited inhibitory centre is aroused by stimuli radiating from some other centre than the respiratory, perhaps from the vasomotor area. In any case, in this sinus slowing, as in the regular slowing, the contractions of the heart are normal in character, the only departure being a slower generation of impulses by the rhythmogenic centre. I have already mentioned that careful measurements show that in the ordinary slowing from digitalis variations in the rhythm corresponding to the respiration are present. The sinus irregularity is merely an exaggerated form of this induced by larger doses of the drug in susceptible cases.

In other instances in which digitalis is pushed, an irregularity of another kind is developed; the impulses are generated regularly, but fail to reach the ventricle owing to their not being transmitted along the bundle of His. There is, in fact, a partial heart block. The features of this condition have been so fully discussed of late years that it is unnecessary to describe them here. You know how the auricle continues to beat regularly, but every now and then an impulse fails to reach the ventricle and a pulse beat is dropped. This has been noted by a number of observers in the use of digitalis, and has generally been ascribed to the conduction of the bundle having been reduced by the inhibitory stimulation of the drug. It appears to occur especially in cases in which the transmission of impulses is already impaired by disease, as is indicated by the interval between the auricular and ventricular contraction being much prolonged, but it may be induced by digitalis when no impairment of conductivity was detected before; while on the other hand, Mackenzie gives a case in which the conduction was very slow before digitalis, and did not seem to be further depressed by it. This failure of conduction from the auricle to the ventricle under digitalis is universally ascribed to the inhibitory action of the drug, and in fact, has been seen to disappear under atropine, which removes the inhibitory action of the cardiac vagus. This may seem proof positive and I am not prepared to deny that in these cases the inhibition is the potent

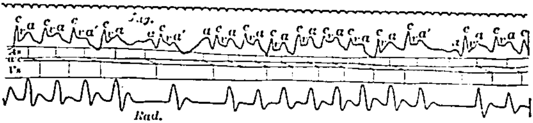

FIG. 2.—Tracing of jugular (upper) and radial pulse (lower) in patient under digitalis, showing occasional failure of the ventricle to contract; a diagram is interposed showing this more clearly. (Mackenzie.)

factor in the irregularity. At the same time, I am not satisfied that it is the only one; for in animal experiments I have seen repeatedly, in fact it is the general rule at a certain phase of the action, that complete block is elicited, the auricles and ventricles beating independently, and yet this block is independent of the inhibitory action for it occurs after large doses of atropine. I should not be surprised to find that in man also the conductivity of the bundle is impaired by direct action on it and the further lowering of its activity by the inhibitory factor induces the block with which we are all familiar. This irregularity is often accentuated at certain phases of the respiration at which the constant inhibitory influence of the drug is reinforced by the stimulus radiating from the respiratory centre.

These two irregularities from excessive inhibition may occur spontaneously in treatment with digitalis. When they are not present, they may sometimes be elicited by further stimulation of the inhibitory mechanism, direct or reflex. Thus slight pressure on the vagus nerve in the neck is often sufficient to demonstrate this action under digitalis. Latent irregularity may also be discovered in some patients by giving them water to sip. Each time water is swallowed the pulse is remarkably slowed and either sinus arrhythmia or partial block occurs. Here, I presume, the excitation of the centres governing swallowing radiates to the centre for cardiac inhibition and arouses it to excessive action. As a measure of the recovery of our patients, we often send them up a flight of stairs and then record the pulse rate immediately afterwards. In a number of cases we have noted that the slowing which follows the initial acceleration of the pulse, went on to irregularity, either sinus or block according to the case; in these there was no irregularity except after this slight exertion.

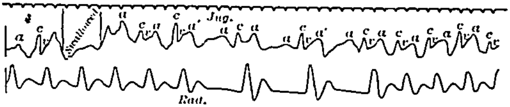

FIG. 3.—Tracing of jugular (upper) and radial pulse (lower) under digitalis in which the rhythm is ordinarily regular, but in which partial block is induced by swallowing. (Mackenzie.)

There can, therefore, be little question that the action of digitalis on the inhibitory mechanism which has been investigated in animals, is exerted in a very similar way in a certain proportion of human patients treated with this drug. In moderate degree the inhibition effect slows the pulse, in larger development it may lead to irregularities or, at any rate, favor their development. The sinus irregularity and the partial block are always preceded and accompanied by slowing. All three features may be developed in the same patient, the sinus irregularity occurring at one time and block at another.[4] I may add that I elicited and described the phenomena now known as sinus arrhythmia and block by digitalis in the dog many years ago and demonstrated that they were inhibitory in nature. That they occur on stimulation of the vagus in animals is common knowledge.

When we come to look for evidence of the direct action of digitalis on the heart muscle in these cases the position is a much more difficult one, for our present methods of heart examination give very inadequate information of changes in the contractility and tone. I may remark in passing, that here history is repeating itself, for direct proof of the inhibitory action of digitalis was available in experimental investigations on mammals many years before it could be shown to act on the muscle directly. The essential feature of digitalis action in animals in small doses is the stronger beat of the ventricle. In patients, this is difficult to demonstrate. It is true that the apex beat may be considered stronger and the pulse beat larger, but no method of measuring these satisfactorily has yet been devised. And even if this were possible, another difficulty has to be faced; for the heart is often slower, and this in itself would tend to strengthen the contraction of the heart and would increase the stroke of the pulse. So that it is impossible at present to demonstrate directly that the contractility of the heart muscle is increased. Another feature observed in animals experimentally is the lessened relaxation in dilated hearts, and there seemed some hope that this might be demonstrable clinically. But in a number of cases in which we attempted to satisfy ourselves on this point, we could make out no change in the area of cardiac dulness, even when digitalis improved the general condition quite satisfactorily. And the apex beat did not move inward. I do not deny that in some cases these alterations in the physical signs are observable, but in our experience such a change is not by any means always apparent, even when digitalis is exercising its full beneficial effects. In a certain number of cases, however, indirect evidence of the action on the heart muscle may be offered. Thus in a number of patients digitalis failed to reduce the pulse rate or to induce any symptom which could be ascribed to the inhibition; yet in these cases, the embarrassment of the breathing became less, anasarca disappeared and the general condition seemed improved, and this relief must, therefore, be attributed to the only other factor which we know—the muscular action. Similarly, in some cases in which helleborein was given (in ½-grain doses t. d. s.), the pulse was not slowed, and no other symptom of inhibition was elicited, but throbbing of the heart was complained of by some patients, and this also seems to indicate change in the muscular contraction independent of the inhibition. I allow that this evidence is very unsatisfactory compared with that given for the inhibitory action, but more adequate proofs can only be expected when more satisfactory methods of measuring the strength of the cardiac contraction are available. At present, we can measure only the rhythm.

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[4] The fact that the slowing, the sinus arrhythmia and block are so frequently seen together while the last two arise from different parts of the heart, suggests that in these patients the abnormality consists in unusual sensitiveness of the inhibitory centre rather than in a low degree of resistance of the heart to inhibition. For there is no reason why both the rhythmogenic centre and the bundle of His should so often show the same variations. And this would imply that the absence of slowing in most cases is due to failure of the inhibitory centre to react to the drug.

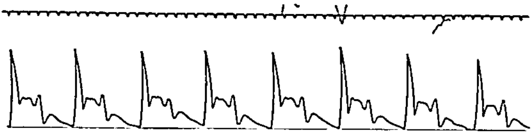

FIG. 4.—Tracing of radial pulse under digitalis, showing extrasystole after each normal pulse movement (continuous bigeminus).

Another feature which occurs in animal experiments is the increased excitability of the heart muscle, which makes itself apparent by a tendency to premature contractions or extrasystoles in the ventricle, or auricle and ventricle. These we have very often elicited in patients under full doses of digitalis in the form of more or less frequent extrasystoles (Fig. 4). This augmented irritability is unquestionably the result of the direct muscular action of the drug for, though its occurrence may be favored by slowing of the heart, it often arises in patients who do not present this feature in marked degree. Wenckebach states that extrasystoles may disappear under digitalis medication, but this form of irregularity is so capricious in its appearance that I am not disposed to regard digitalis itself as curative. Another feature which has repeatedly occurred in our cases, although more rarely, is pulsus alternans, in which the pulse beats and also the apex beats are alternately large and small without any difference in the interval between them. This form occurs especially after an extrasystole or after a pause of some duration (sinus slowing) and then gradually becomes less marked and disappears. It is met with in untreated cases of heart disease and is generally regarded as evidence of a serious reduction in the contractility. The most satisfactory explanation is that of Wenckebach, who regards the weak beat as the result of the prolonged activity of the preceding strong contraction. It may, in fact, be regarded as a condition in which the recovery of energy by the heart is retarded, while the dissipation of energy during the contraction is not changed to the same extent or perhaps is unaltered. It may be suggested that digitalis by increasing the contraction power of the heart without a corresponding effect on the restorative function may occasionally tend to favor the development of this abnormality in hearts which are predisposed to it.

Turning to the second group of cases, those in which the node of Keith and Flack has lost its leadership, and the rhythm arises from some other part of the auricle, we find that digitalis has a much more striking effect. In fact it may be questioned whether it would have attained its position as *the* cardiac remedy had it not been for its efficacy in this condition, in which its exhibition is often followed by a truly wonderful improvement. The commonest form of this abnormal rhythm is that known as auricular fibrillation, and there is every reason to infer that a number of Withering's cases were of this description.

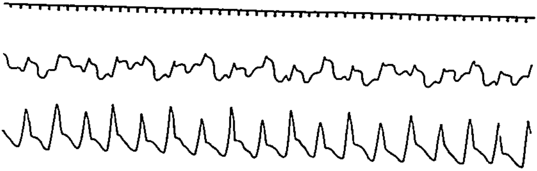

FIG. 5.—Tracing of radial pulse and apex (upper) under digitalis, showing alternation in artery and apex.

In this condition, which has long been known in animals, the auricle is distended and a continual tremulous movement occurs in its fibers, but there is no coördinated contraction, the fibers moving quite independently of each other. Irregular impulses are constantly discharged to the ventricle, which responds with a very rapid and quite irregular rhythm. In man, the condition was first defined by Mackenzie's observations on it, and is characterized by extreme irregularity of the pulse and by the absence of all signs of auricular activity. Its true pathology has only been determined recently. In our cases of this condition, the exhibition of digitalis was generally followed by rapid improvement. It is true that it did not restore the normal rhythm, but the symptoms of heart failure disappeared much more rapidly than in cases of the first group in which the normal rhythm was preserved. And coincidently with this improvement in the general symptoms the rate of the pulse fell from 120-150, to 60-70 or less.[5] The pulse remained irregular, but the irregularity was less marked (Fig. 6), and the beats were much stronger; the dyspnœa was relieved and the other symptoms of distress underwent marked improvement. The patient was often able to return to his work if it was not of an exhausting nature.

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[5] To ascertain the heart rate with even approximate accuracy in these cases, a record of the pulse must be taken or the heart sounds counted.

The most striking objective symptom was the fall in the pulse rate, which offered a marked contrast to that observed in the first group of cases. In these, in which the rhythm arose from the normal position, only about 30 per cent. of the cases reacted to digitalis with slowing, while 11 out of 12 of our cases of fibrillation, or 90 per cent., showed unmistakable slowing. In the twelfth there was fever present and no slowing occurred. The pathology of the condition suggests that this slowing is due to fewer impulses reaching the ventricle from the auricle. The condition of the last chamber is unchanged as far as our means of observation teach us, and there seems no other plausible explanation of the fall in the pulse rate than a diminution in the impulses passing the bundle of His. Moreover, in some rare forms of auricular delirium the pulse though completely irregular is not accelerated, and here there is reason to believe that the impulses from the auricle are partially blocked in their passage to the ventricle; in these cases digitalis does not slow the heart nor cause any marked improvement. Wenckebach has shown that stimulation of the inhibition by pressure on the vagus in the neck in auricular fibrillation induces the same slow pulse as occurs under digitalis, and in a case in which this procedure was ineffective, digitalis also failed to improve the rhythm. One is, therefore, tempted to

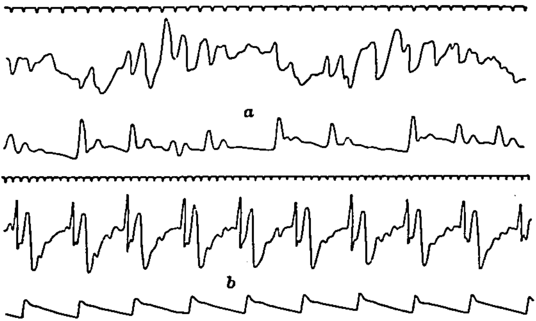

FIG. 6.—Tracing of the jugular (upper) and radial pulse (lower) in a case of fibrillation of the auricle (a) before treatment, (b) after treatment for some weeks with digitalis.

attribute the remarkable effects of digitalis in the ordinary forms of auricular fibrillation to its inducing a partial block of His' bundle[6] and thus relieving the ventricle from the continual bombardment with impulses from the auricle; that is, the digitalis action here would appear to be pure inhibition. And this explanation is supported by our experience in a number of cases in which the distress disappeared as the pulse fell, and when the treatment was given up for a few days the pulse accelerated, and almost step by step with the acceleration of the pulse, the dyspnœa returned.

In several cases the question has been further tested by the injection of atropine in sufficient quantities to put the inhibition out of action. For example, in a case of fibrillation in which the pulse was originally 150-170, but in which it had been reduced by digitalis to 60-70 per minute, $\frac{1}{50}$-grain atropine sulphate hypodermically accelerated the pulse to about 120. This seems to suggest that the inhibition was a large factor in the effect, though not the only one, for though the pulse was much accelerated by atropine it did not regain its original rate. In another case in which the original rhythm was about 150 per minute, it was reduced to about 50-60 by large doses of digitalis (15 minims four times a day). The patient left the hospital and continued to take digitalis as he felt the need of it, gradually reducing it until after some months he found that his pulse remained slow without the drug, and he only took about a drachm when it began to accelerate, about once a week. Yet on giving atropine at this time the pulse at once rose to 150 per minute, that is, to its original rate. In this case there seems no question that the conduction was reduced permanently by inhibition or, rather, that the inhibition had gained a permanent control over the heart, which was absent before the digitalis was given. Whether this is due to the prolonged inhibition to which the heart had been subjected by digitalis in the hospital, or whether the nutrition of the organ had been altered by some other effect of digitalis, *e. g.*, on the heart muscle, I am unable to say. And the fact that our methods give no sufficient indication of the changes in contraction power must render us careful in the interpretation of the symptoms. But I think I am safe in stating that we have no definite evidence that digitalis exerts any action apart from the inhibition in these cases of auricular fibrillation and that the proved fact of inhibition explains all the features observed.

When digitalis is pushed in auricular fibrillation it often reduces the rate still further to 40-50 per minute and induces "coupled beats;"

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[6] Another possible interpretation may be suggested: In auricular fibrillation inhibition makes the tremor of the auricle finer in character, and perhaps the impulses transmitted to the bundle of His are weaker and thus fewer of them reach the ventricle. Digitalis may, therefore, slow the ventricle by weakening the impulses from the auricle rather than by increasing the difficulties in their passage.

that is, each beat of the ventricle is followed at a very short interval by a second weak contraction and then by a long pause (Fig. 7). The electrocardiograph indicates that the first strong contraction originates in the normal way by an impulse reaching the ventricle from the bundle of His, while the second weak one is a true ventricular extrasystole. In one of our cases in which "coupled beats" were present, atropine accelerated the rhythm of the ventricle by improving the conduction in the bundle and as the rate increased the coupled beats became fewer and finally disappeared. This suggests that the irregularity was at any rate, in part the indirect result of the slow rhythm which allowed the irritability of the ventricle time to develop, and that here the extrasystole resulted indirectly from the inhibition.

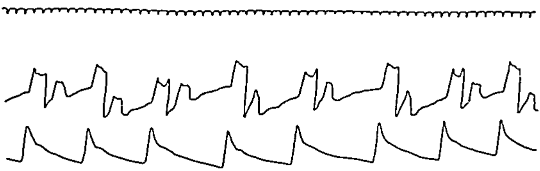

Fig. 7.—Tracing of apex beat (upper) and radial pulse (lower) in fibrillation treated with large dose of digitalis. In the apex tracing an extrasystole is seen to follow each normal beat (coupled beats or continuous bigeminus). These are too weak to cause a pulse in the radial.

In animals I have often observed auricular fibrillation occur from very large quantities of digitalis from excessive stimulation of the auricle muscle. It is of interest to note that in two cases we have met with the same phenomenon in patients. In one of these digitalis had been given for some time without slowing the pulse which maintained a rapid regular rhythm. Suddenly the rate fell to about 70 and the heart became quite irregular. All evidence of auricular activity disappeared—no *a* wave in the jugular pulse, disappearance of a presystolic murmur which was formerly present—in fact a typical picture of auricular fibrillation under digitalis was presented. With equal suddenness the fibrillation disappeared and the former rapid normal rhythm was restored, when the drug was abandoned.

Here it might be supposed is certainly an instance where the muscular action was the cause of the irregularity, for the irritability of the heart muscle is augmented by the direct action and culminates in fibrillation. I would not deny the explanation, but I may remind you that fibrillation may occur from inhibition, so that it is possible that here also the action is central.

Apart from auricular fibrillation we have met two cases in which the rhythm was given by the auricle, but which it was quite regular though extremely rapid. In these digitalis reduced the rhythm quickly and brought relief from the dyspnœa and other symptoms. In one of them the slowing was interrupted by short phases of what seemed auricular fibrillation, but these became less frequent as the heart rate fell to the normal. The slowing of the pulse in these cases was comparable to that observed in cases of auricular fibrillation, and the question arises whether it was brought about in the same way by a diminished conduction of impulses from the auricle to the ventricle, or whether the actual discharge from the abnormal point in the auricle disappeared under the inhibitory action of the drug.

In any case the efficacy of digitalis and its allies in disorders of the heart arising from auricular hyperactivity is very striking, and raises the question whether the chief usefulness of the drug does not consist in its protection of the ventricle from the too exigent demands made on it by the auricle.

I have given you some instances in which the inhibitory factor seems to play an important, perhaps a dominant part, in the effects of digitalis in therapeutics. Let me remind you of one in which the muscular action alone is desirable. In partial or complete block the indications are to accelerate the ventricle and relieve the symptoms of arrest of the circulation which culminate in the Stokes-Adams syndrome. Bachmann, I think, was the first to utilize the muscular action of digitalis for this purpose, but it might be preferable to employ a member of the series without its inhibitory action, and in future cases I would suggest the use of helleborein or of a mixture of helleborein and digitalis.

The question as to the respective roles played by the inhibitory and the muscular factor in digitalis is not of theoretical interest only. For if the therapeutic effects are due to inhibition only, they might be elicited by other drugs which do not possess the unpleasant effects on the alimentary tract which present themselves under digitalis. On the other hand, if the muscular action is the essential factor, it might be possible to discover a drug possessing this without the inhibitory effects. In any case it seems desirable that we should be able to vary the proportions of these two factors, for there is no reason to suppose that digitalis presents the exact combination which is suitable in all cases. We, therefore, have treated a number of cases of heart disease with aconite and aconitine, which is reputed to slow the human heart by stimulation of the vagus centre, but has not the digitalis action on the cardiac muscle. But Dr. Price, who has carried out this investigation, finds that aconite does not deserve its reputation in this respect, for it failed to slow the heart even when pushed until unpleasant symptoms appeared; yet these cases afterward responded to digitalis by slowing. On the other hand, we have tried helleborein which possesses the muscular effect of digitalis without its action on the inhibition, but the results were not satisfactory for although no slowing occurred no definite improvement followed in our cases. This may be partly owing to the fact that helleborein tends to cause diarrhœa when given in adequate doses, and we intend to continue its investigation further.

These experiences have led us to make a systematic comparison of the members of the digitalis series in therapeutics. As yet we have taken up chiefly the three common members, digitalis, strophanthus, and squills, and these we have used in the form of the tinctures, as this seemed to be of more importance than the pure principles, which are comparatively seldom employed. Our method is to give digitalis tincture first and push it until it fails to induce further improvement and unpleasant symptoms arise; then all medication is suspended for ten days or more and the patient very often relapses to his former state. Tincture of strophanthus is then given in the same way, again an interval is allowed and finally squills is prescribed; the order is not always the same of course. We have made some interesting observations for the details of which I must refer to a paper by Turnbull which will appear soon from Mackenzie's clinic. Among these I may mention that we find the tincture of digitalis (B. P.) to be nearly twice as powerful as that of squills or strophanthus, although they have been used in the same dose for many years.[7] Both the therapeutic effects and the untoward symptoms of squills or strophanthus are only elicited when they are given in nearly twice the dose of digitalis.

In reading Withering's account of his treatment one is struck by the fact that he always induced vomiting as soon as possible and then continued his treatment with smaller doses. We have not gone so far as the pioneer, but we have found again and again that the best results are obtained only by the largest doses which can be given without gastric and intestinal symptoms. The dose which we find advisable is a dram to a dram and one-half per day of digitalis tincture, or a dram and one-half to two drams of tincture of squills or strophanthus (B. P.). This, of course, is twice as much or more than is ordinarily prescribed, and I must confess that not infrequently there arises nausea and occasionally vomiting, or sometimes severe headache from the higher dose. But on the other hand, we have patients taking a dram of digitalis per day for months and sometimes going to work under this regime.

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[7] These relations hold only for the tinctures of the B. P. The tincture of strophanthus (U. S. P.) is four times as strong as that of the B. P., and according to our results the efficient dose of this would be about one-half that of the tinctura digitalis (U. S. P.) and this is the proportionate dose actually suggested in the U. S. P. The tincture of squills (U. S. P.) on the other hand, is only one-half the strength of that of the B. P., and our results would suggest it being given in three or four times the dose of tinct. digitalis U. S. P.

There is no question that digitalis and its allies are too much feared by the medical profession. The "cumulative" action has been held over us as a bogey for so many years that many prescriptions contain this valuable drug in harmless and useless doses. *Non nocere* is a good rule, but *prodesse* is a better, and tincture of digitalis in two minim doses three times a day approaches the line of purely expectant treatment.

As regards their relative usefulness there is little difference between these three drugs. We get the same beneficial results and the same undesirable ones as regards the heart, and a patient who shows symptoms of heart block under digitalis, suffers from the same irregularity under squills or strophanthus, while when extrasystole is induced by one it follows from all. Strophanthus is often said to have less tendency to raise the blood pressure than digitalis, but in our patients neither induces any rise of pressure and in some both cause an equal fall. There is, on the whole, rather less tendency to headaches, nausea, and vomiting under strophanthus and squills than under digitalis, but the difference is not very marked and headache is caused in some cases by all three. Slight diarrhœa has followed the use of squills more than the others, and strophanthus also tends to cause this more than digitalis. This tendency to diarrhœa is still more marked from the use of helleborein and apocynum which we have begun to work upon.

In animal experiments, one of the characteristic effects of digitalis medication is the rise of blood pressure, which arises in part from the heart action, in part from a constriction of the arterioles. In patients the blood pressure is rarely augmented by digitalis and may in fact fall, as the general improvement sets in. This is, I think, due to the much greater efficiency of the vasomotor mechanism in man, which has been developed to permit of his assuming the erect attitude. As the heart fails in disease, the organ which first suffers is the brain; but anemia of the brain is promptly remedied by constriction of the abdominal vessels, by which the blood is again directed to the head areas. If, now, digitalis is given and the heart action improves, the first effect would be to increase the blood supply of the brain, and this leads the sentinel in the medulla to relax its vigilance, the mesenteric vessels are allowed to relax and the improvement in the heart may thus be coincident with lowered blood pressure. In our experience there is no significant increase in the urine except when dropsy is present.

In the course of this investigation I have been struck by the small amount of accurate knowledge that we possess as to practical therapeutics. My experience has been almost exclusively in the laboratory and perhaps I have expected too high a standard in the clinic, but in this field of cardiac tonics alone I see an endless vista of questions to be solved in the clinic if only accurate observations are available. There seems to me to be no field in which painstaking work is more required and in which the prospects of success are more promising than in clinical therapeutics. I would commend the cultivation of this study to any one who wishes to add to the general store of medical knowledge and at the same time to devote himself to some line of work which will bear upon his own future work. But we have enough of inaccurate therapeutics already; what is needed is not a statistical compilation, but an accurate study of each individual case and a careful and, if you will, an experimental investigation of each feature presented.

PERSONAL EXPERIENCES WITH THE USE OF SALVARSAN (DIOXYDIAMIDOARSENOBENZOL, OR "606") IN THE TREATMENT OF SYPHILIS.[1]

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Case XVIII.—S. M. K., aged twenty-three years, acquired lues three years ago. Following the appearance of the secondary roseola, the patient was given a course of injections of salicylate of mercury. The injections were badly borne, causing symptoms of mercurial poisoning. From time to time mucous patches appeared in the mouth, and headache was an almost constant symptom. After a freedom from medication for more than six months, the patient was given one injection of bichloride of mercury (2 per cent., 10 minims), which was followed by bloody diarrhœa, nausea, vomiting, and salivation lasting for about a week. No further attempt at mercurial medication was made. In October, 1910, the Wassermann test was positive. In November, 1910, the patient developed mucous patches on the tonsils. The Wassermann reaction was positive. On November 15 the patient received 0.5 gram of an alkaline solution of "606" into the right buttock. The injection caused pain throughout the night following the giving of the drug, which was readily controlled by morphine. The patient was out of bed the next day, and the further course of the case was uneventful. The mucous patches on the tonsil disappeared within twenty-four hours. The patient on January 15 was free from all signs of lues. The Wasserman reaction was negative. On February 1, 1911, the reac-

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[1] Concluded from page 429.